Supplementary Material C

Results of pairwise meta-analyses comparing intervention groups against TAU

Initially pooled treatment effect estimates were computed including only studies involving a TAU control arm (Table C1). The analyses were stratified by intervention groups.

Overall 52 exercise interventions (43 studies) involving 2352 participants were compared to TAU. The average size for each comparison was small (median total sample size per comparison of 32). As a result, individual comparisons suffer from low power and may introduce small sample effects into the estimation of the pooled effect size. This was confirmed by an asymmetrical funnel plot below (supplementary material) and Eggers test (bias -1.5, t=-1.87, p=.067). Excluding 5 outlier studies,[1] the overall treatment effect of exercise was estimated to be moderate, however, statistical heterogeneity was substantial. Differences in treatment effect across exercise subgroups accounted for some of this heterogeneity. Balance exercise had the largest treatment effect of the exercise subgroups. Further subdividing the general exercise interventions into those in or not in an aquatic environment made no different to the treatment effect estimate (SMD 0.39 vs 0.50, respectively).

Overall 28 behavioural interventions (27 studies) involving 2002 participants were compared to TAU. The average size for each comparison was small (median total sample size per comparison of 50). As a result, individual comparisons suffer from low power and may introduce small sample effects into the estimation of the pooled effect. A funnel plot

[1] Kargafard et al. (2012) & Kargafard et al. (2017) included a TAU control arm with a surprising deterioration in fatigue between baseline and follow up; Razazian et al (2016) showed surprisingly large improvements from baseline for both treatment groups and a small deterioration in fatigue in the control arm; Cakt et al. (2010) included a resistive exercise intervention that performed significantly worse than the TAU control arm and a further combined exercise arm; Sangelaji et al. (2014) included a TAU control arm with a surprising deterioration in fatigue between baseline and follow up that inflated.

(supplementary material) provided some indication of small study effects for behavioural interventions, though Eggers test was non-significant (bias -0.7, t=-1.27, p=.215). The overall treatment effect of behavioural interventions was estimated to be small to moderate. Statistical heterogeneity was relatively low. Considering behavioural intervention subgroups, treatment effects were small to large with considerable variation between subgroups. Pooled estimates for CBT and relaxation and biofeedback interventions were moderate to larger. Whereas pooled estimates for energy conservation, neurocognitive rehabilitation and education or information interventions were all small to moderate. Heterogeneity was low for all subgroups. Further, subgroups indicated no substantial difference comparing high versus low intensity CBT (SMD 0.62 vs 0.51, respectively). Only 1 study considered energy conservation incorporating CBT elements thus a comparison to studies not incorporating CBT elements could not be assessed.

Overall, 12 combined behavioural and exercise or physical activity interventions (12 studies) involving 939 participants were compared to TAU. The average size for each comparison was moderate (median total sample size per comparison 68.5). A funnel plot provided no indication of small study effects for behavioural interventions and Eggers test was non-significant (bias 0.30, t=0.34, p=.743). The overall treatment effect of combined interventions was estimated to be small to moderate. Considering combined intervention subgroups, treatment effects were small for interventions combining behavioural interventions, such as motivational interviewing, with exercise and physical activity promotion, and also for physical rehabilitation programmes.

Table C1. Pooled estimates of treatment effect compared to TAU, heterogeneity, and quality of the evidence (GRADE).

	$N_{comparisons}$	$N_{participants}$	Median	SMD	95% LCI	95% UCI	I^2	**Quality of the evidence (GRADE)**
Exercise interventions (excluding outliers)								
Aerobic	15	475	30	-0.41	-0.62	-0.22	18.50%	⊕⊕⊕⊖ **Moderate[a]**
Balance	3	168	67	-0.87	-1.18	-0.55	0.00%	⊕⊕⊕⊖ **Moderate[b]**
Resistive	4	161	32.5	-0.46	-0.77	-0.15	0.00%	⊕⊕⊕⊖ **Moderate[b]**
Flexibility	1	38	.	.	.	.	.	n/a
Combined exercise	12	767	41.5	-0.35	-0.50	-0.20	68.20%	⊕⊕⊖⊖ **Low[a,c]**
General	11	544	34	-0.47	-0.65	-0.30	32.60%	⊕⊕⊕⊖ **Moderate[a]**
Overall	46	2153	32	-0.44	-0.53	-0.35	42.5%	⊕⊖⊖⊖ **Very Low[a, c, d]**
Behavioural interventions								
Energy conservation	6	632	108.5	-0.19	-0.35	-0.03	0.00%	⊕⊕⊕⊕ **High**
CBT	9	775	50	-0.54	-0.69	-0.40	3.40%	⊕⊕⊕⊕ **High**
Neurocognitive rehab	6	269	41.5	-0.24	-0.51	0.02	12.30%	⊕⊕⊕⊖ **Moderate[b]**
Relaxation & biofeedback	5	217	48	-0.53	-0.80	-0.26	0.00%	⊕⊕⊕⊖ **Moderate[b]**
Emotional expression therapy	1	60	.	.	.	.	.	n/a
Education or information	1	49	.	.	.	.	.	⊕⊕⊕⊖ **Moderate[b]**
Overall	28	2002	50	-0.37	-0.47	-0.28	12.40%	⊕⊕⊕⊖ **Low[c, d]**
C*ombined interventions*								
Behavioural plus exercise	8	728	94.5	-0.28	-0.43	-0.13	0.00%	⊕⊕⊕⊕ **High**
Physical rehab	4	211	43	-0.16	-0.44	0.11	0.00%	⊕⊕⊖⊖ **Low[a, b]**
Overall	12	939	85	-0.25	-0.38	-0.12	0.00%	⊕⊕⊕⊖ **Moderate[d]**

a: Most information is from studies with inadequate allocation concealment or incomplete accounting for outcome data.
b: Total sample size is small
c: Wide variation in effect size exists across studies or large I-squared indicates large proportion of the variation in effect size due to among-study differences.
d: Small sample effect on the estimated effect due to asymmetrical funnel plot.

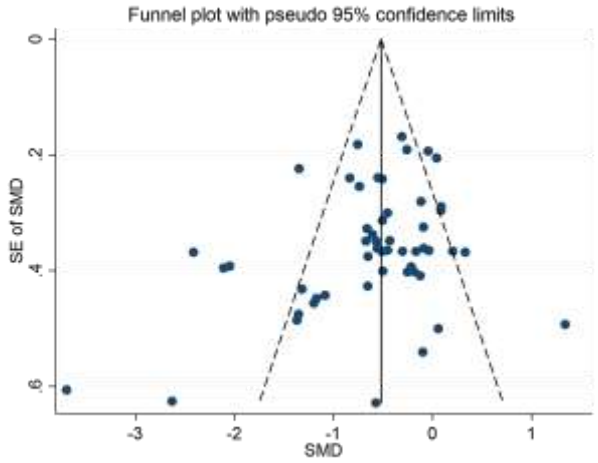

Figure C1. *Funnel plot for exercise interventions (including outliers).*

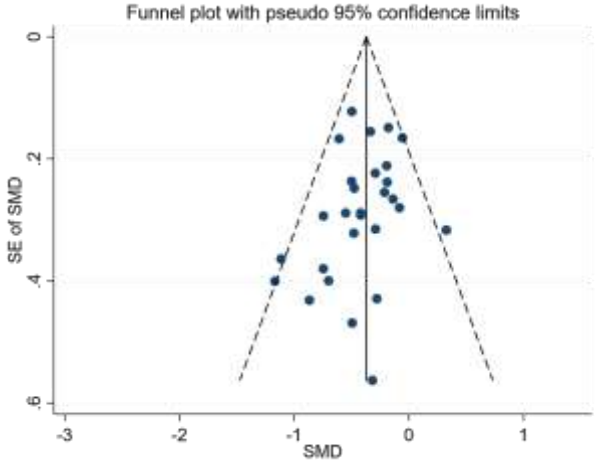

Figure C2. *Funnel plot for behavioural interventions.*

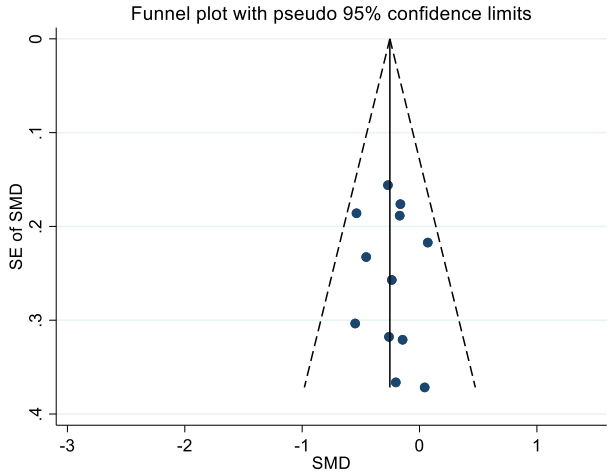

Figure C3. *Funnel plot for combined interventions.*

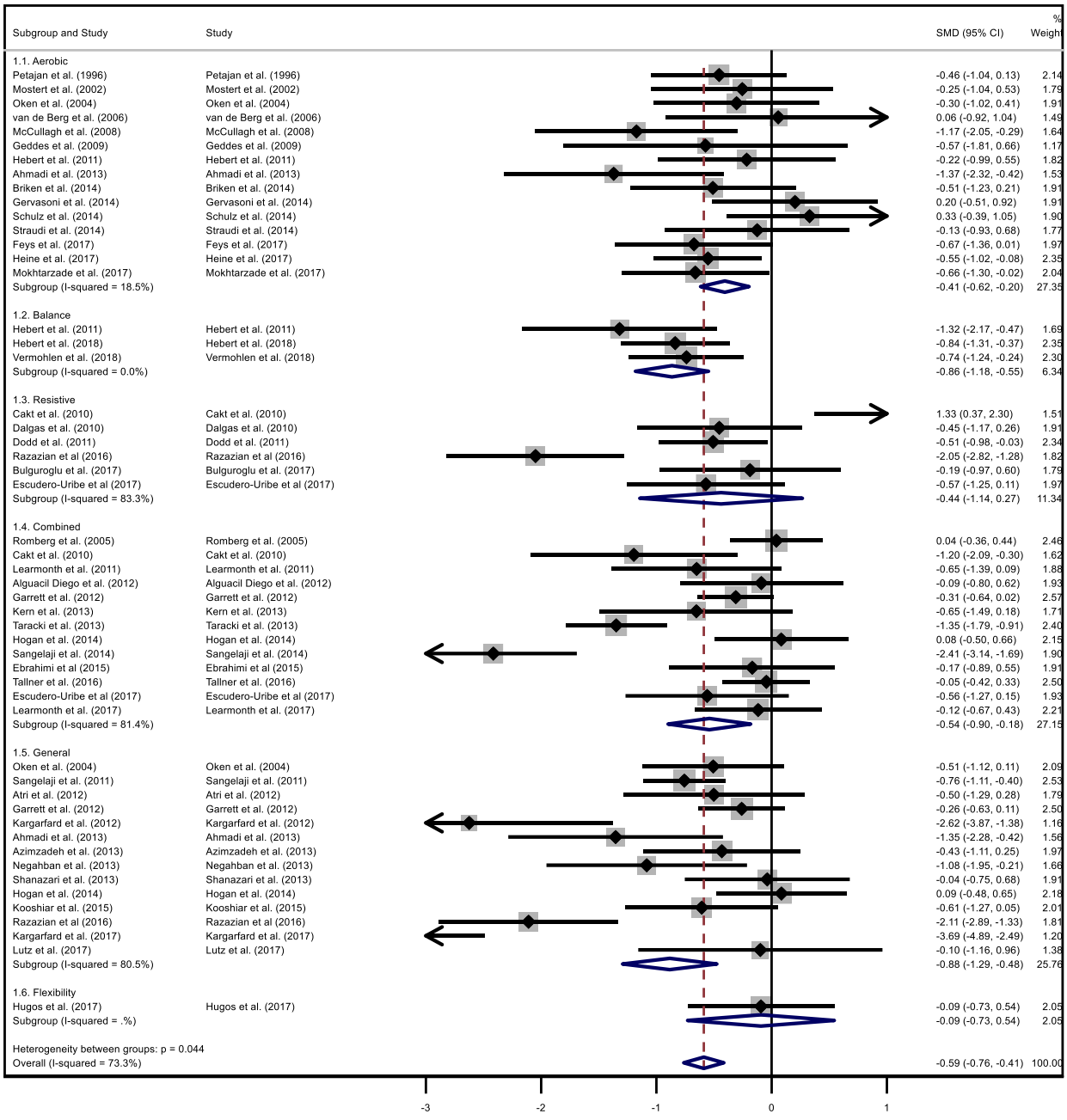

Figure C4. *Forest plot of exercise interventions compared to TAU.*

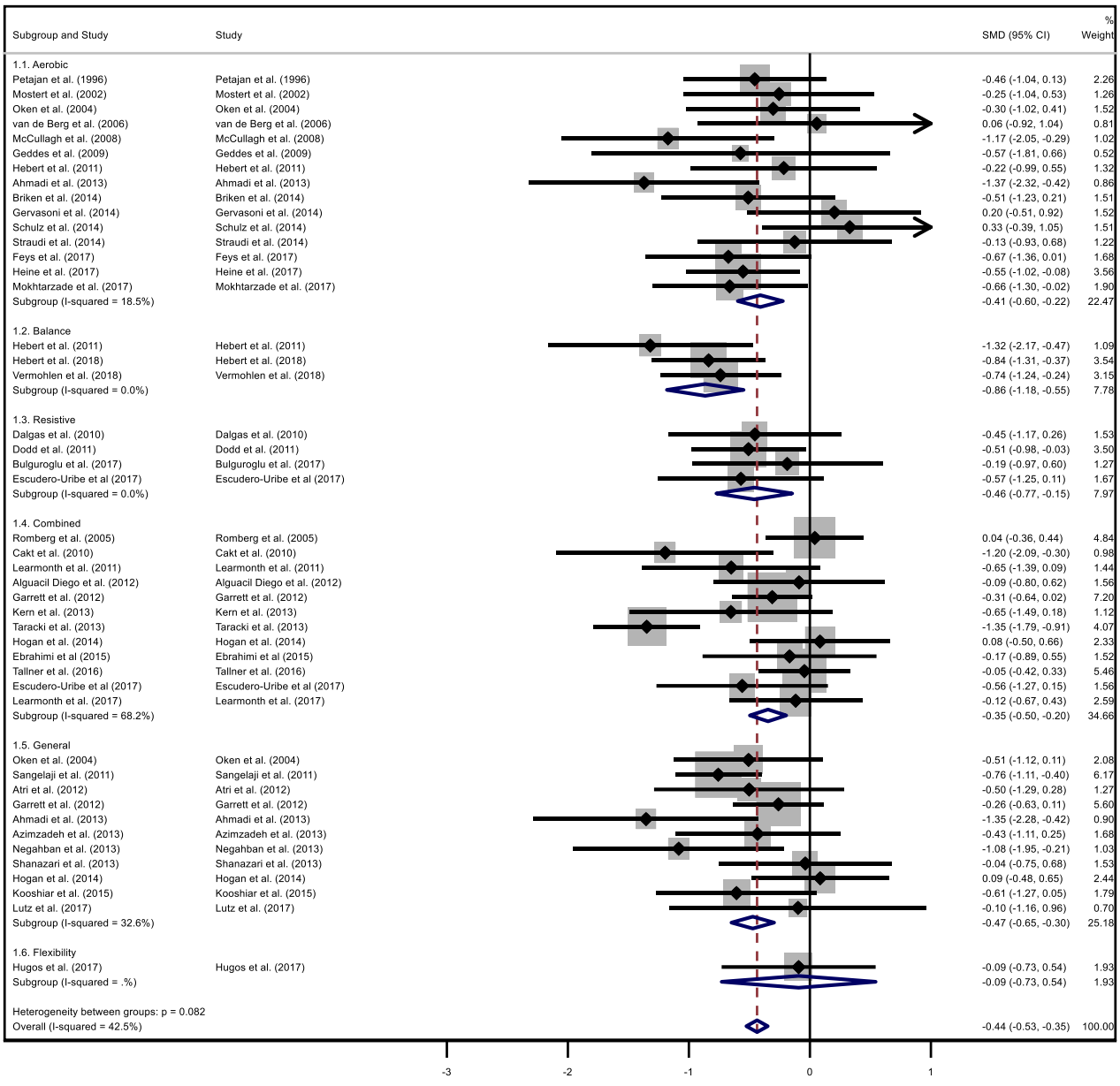

Figure C5. *Forest plot of exercise interventions compared to TAU, excluding outliers.*

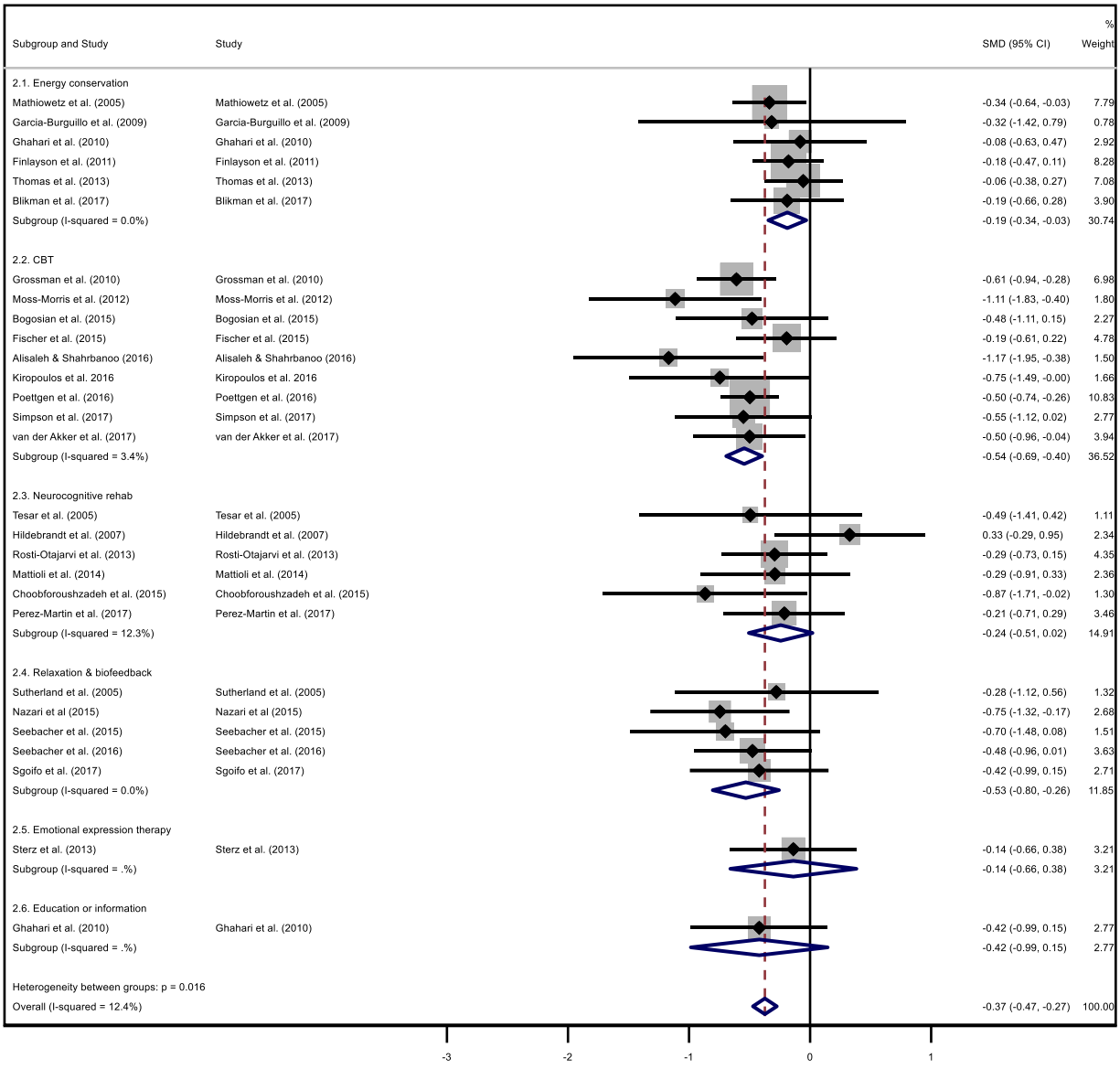

Figure C6. *Forest plot of behavioural interventions compared to TAU.*

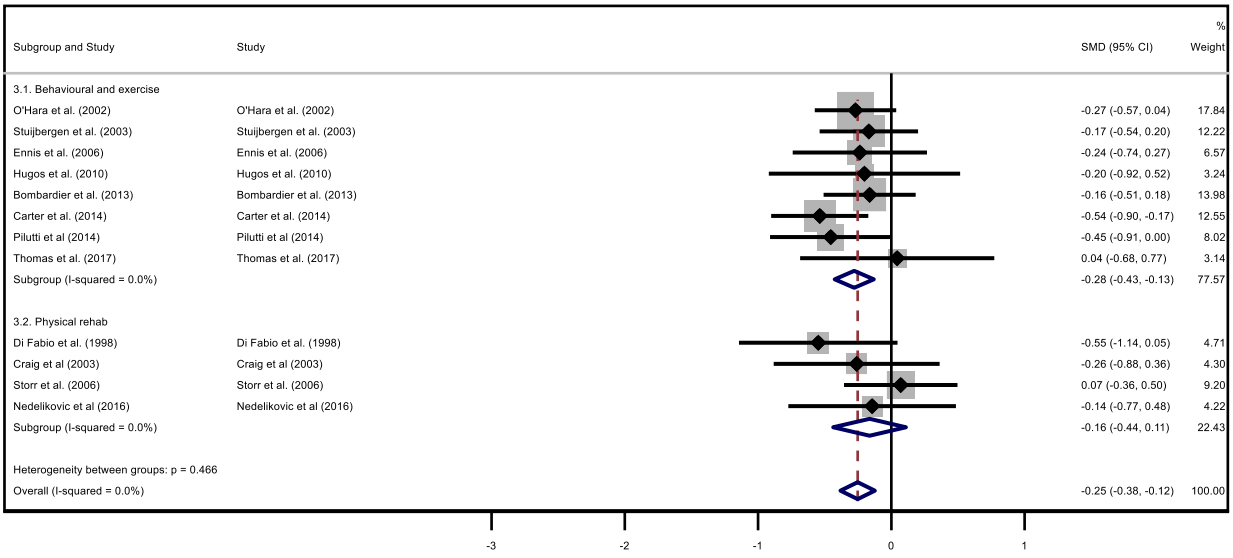

Figure C7. *Forest plot of combined interventions compared to TAU.*